CHAPTER 1

The Anxious Brain

Scientists all over the world are now studying the anxious brain. Since the first edition of this book was published in 1998, understanding of the biology of anxiety has changed so profoundly that this chapter has been completely rewritten. It is no accident that so much creative energy, and so much money, is now being spent on the anxiety problem. As recently as the 1980s, the anxiety disorders were thought to be both uncommon and virtually untreatable. Anxiety disorders were considered by most mental health practitioners and researchers to be trivial compared to the "major" mental disorders—the psychotic disorders such as schizophrenia and major depression. People suffering from anxiety were called, disparagingly, "the worried well."

Attitudes within the mental health field toward clinically significant anxiety have changed completely for two reasons. First, modern epidemiological studies of mental disorders, using more scientific diagnostic categories, have shown that the anxiety disorders are the most widespread or prevalent of all of the mental disorders, exceeding even major depression and all of the other affective disorders combined. Second, studies of the economic costs of major groups of mental disorders have shown that the anxiety disorders are far from trivial. Anxiety disorders produce higher costs to society than any other class of mental disorders. Most of this high cost is the result of lost productivity at work.

As a direct result of this new knowledge, research funded by the National Institutes of Health and by major pharmaceutical companies has increased. Today government and private research together devote hundreds of millions of dollars a year to the study of anxiety.

These dramatic changes offer new hope to people who suffer from anxiety problems as better treatments are being developed and brought into practice. An example of these promising developments is the explosive growth of the use of new medicines to treat anxiety. Another example is

the greater appreciation for the specific and effective form of nonmedication therapy for anxiety problems. This form of treatment is called cognitive-behavioral treatment (CBT). The uses of better medicines and better psychological treatments are at the heart of this book.

All three of us have been at the center of these important new developments through our active work with the Anxiety Disorders Association of America (ADAA). ADAA has been the biggest factor in showing that the anxiety disorders are not only common and serious but, even more important, that they can be treated successfully. The ADAA has successfully linked research, practice, and consumer to the benefit of all three.

For more than two decades, we have worked with many pharmaceutical companies in developing new medicines and in finding new uses for some older medicines in the treatment of the anxiety disorders. Together we have conducted hundreds of sophisticated double-blind clinical trials of medicines in the treatment of the anxiety disorders. In this work we have been joined by researchers in all parts of the country and around the world as the anxiety disorders have become one of the most active areas of research in contemporary medicine. In our clinical practices we use these new pharmaceutical advances and the ever-improving cognitive-behavioral treatment to our patients.

In this chapter we look at the explosive growth in understanding of the biology of fear and anxiety. In Chapter 4 we look specifically at the new medicines used in the treatment of anxiety problems.

The Brain Biology of Fear

The brain is made up of more than 100 billion nerve cells connected to each other in a fabulously complex interactive network. Each nerve cell, or neuron, communicates with the many other neurons across tiny spaces, called synapses, between the connected neurons. Messages are carried from one neuron to others by a chemical messenger called a neurotransmitter. Brain biology can be looked at by focusing on the neuronal circuitry used to connect the various parts of the brain with each other and with the organs in the body that express the brain's activity, such as the muscles and hormone systems. In addition to studying the brain's circuitry, the biology of the brain can be understood by studying the neurotransmitters used to send signals from one neuron to the next.

Brain mechanisms of anxiety can be studied in the laboratory by measuring neurotransmitter levels in blood, urine, saliva, and spinal fluid; by

assessing behavior and behavioral responses to pharmacologic challenges to specific neurochemical systems; and by measuring brain structures using neuronal imaging. Useful studies of anxiety have been conducted with both laboratory animals and human subjects.

The Fear Circuits

First let's look at the brain's circuitry that manages fear. From our five senses (sight, sound, smell, taste, and touch) come sensory impulses from all parts of our bodies into the nerve center in the midbrain called the thalamus. This is the brain's sensory clearinghouse. In the thalamus, sensory information of all kinds and from all sources that involve possible danger is split into two major pathways, the high road and the low road. The low road is the fast and automatic road for handling fear. It is designed to respond to possible danger practically instantaneously. Speed is important because signs of danger that can be life threatening can occur on a split-second basis. From the thalamus the sensory inputs travel via the low road to the amygdala and the hippocampus in the temporal lobe of the brain. These brain structures are part of the limbic system that manages memory and emotions. The hippocampus is especially important because it assigns context and emotional meaning to the constant flow of sensory inputs into the limbic system from the thalamus night and day. When the hippocampus identifies a familiar sensory pattern it assigns it a "safe" value if the person's past exposure to that pattern has been benign. When the hippocampus identifies an unfamiliar sensory pattern, or one that has been seen as dangerous in the past, it assigns a "dangerous" value to it. Context is important to the interpretation of sensory inputs over the low road. For example, a loud bang at a Fourth of July fireworks show is considered to be "safe" while a similar noise in the workplace or at home would usually be considered "dangerous." People with a damaged hippocampus often overgeneralize sensory inputs, treating even familiar sensory inputs as unfamiliar and therefore assigning them the emotional meaning of being dangerous.

From the hippocampus, the brain information judged to be dangerous travels to many centers, including the locus ceruleus (LC), the brain's alarm or panic center. This small but very important collection of nerve cells is located in the pons in the brainstem, right in the center of the base of the brain. After input from the hippocampus arrives in the LC, the danger signals in the brain are sent to sites of action to deal with the danger. These recipients of danger messages from the LC include

the hormone center of the brain, the hypothalamus. There danger signals trigger the pituitary hormones associated with responses to stress. Signals go from the LC to many other parts of the brain, including the brain's parietal cortex, which controls the muscles needed for the fight-or-flight responses to danger. The low road brain circuitry functions without conscious thought. It is an emergency automatic pilot that manages immediate responses to danger. This is the primitive, basic brain system to manage fear and danger.

The second brain circuit that manages responses to danger—the high road—also starts with sensory inputs that flow from all parts of the body into the thalamus. However, unlike the low road, this brain circuit routes the signals from the thalamus to the cortex of the brain, the gray matter on the brain's surface. In particular, signals involving fear are carried to the medial prefrontal cortex of the brain. This is the gray matter on the outside of the brain toward the front of the head. This is the part of the brain needed for conscious thought, the formulation of ideas, and the attribution of meaning. The cortex is needed to provide complex analysis of a wide range of sensory inputs, including those that are sent from the thalamus relating to possible danger. The prefrontal cortex is where judgment is added to the mix of brain signals.

The cortex is the most highly developed and largest part of the human brain. An extensive brain cortex is distinctive in humans and closely related animals such as monkeys, although all mammals have some cerebral cortex in their brains. When the cortex is removed from laboratory animals, they lack judgment with respect to possible dangers. Strikingly, they exhibit more fear than when they have functioning cortex material. This experiment shows that the brain's cortex is involved in moderating as well as managing reactions to possible danger.

Both the high road and the low road circuits have important roles in the brain's responses to danger. Once danger is perceived by either road, the brain mobilizes the fight-or-flight response to stress. This involves changes in stress hormones, regulation of breathing and blood flow, and motor responses such as those needed to run away from the danger. These same fundamental brain mechanisms can be mobilized not only by actual dangers but by thoughts of danger that arise from specific cues that have been associated with past dangers. The brain learns from experiences. Past fear reactions are particularly powerful in shaping future behaviors. When an experience has been repeatedly associated with fear and danger, then even the anticipation of that experience, even the

thought of it, triggers the cascade of brain changes associated with danger and stress.

When you take a child to a Fourth of July fireworks display for the first time, the child lacks an adequate context from past experience into which he or she can put what is about to happen. The bright lights and the incredibly loud explosions are, in themselves, terrifying to a young child. Before the sun sets and the fireworks display begins, loving adults (usually that means the child's parents) explain what is to come. The adults hold the child's hand or sit the child in their laps for reassurance. Using the words from the adults, the child's prefrontal cortex reframes the dramatic sensory inputs. From the words of the trusted adults the child's brain changes the sensory signal produced by the explosions in the sky from "dangerous" to "fun." The high road brain circuit receives the low road signal of danger because the sensory input from the fireworks is completely unfamiliar; therefore, it is automatically experienced as dangerous. Thanks to the adults' reassuring words, the high road has additional and vitally important information. The explanation from caring adults changes the meaning of the powerful sensory input. That is the effect of the brain's cortex, the effect of conscious thought that is provided by the high road.

The next time the child experiences Fourth of July fireworks, not only will the cortex offer reassurance but also, unlike the first time the child saw the flashes and heard the booms from the fireworks, the hippocampus will provide information about the context of these dramatic sensory inputs. This important information from the hippocampus on the second exposure will come from the brain's low road fear circuit. Like the information coming from the child's prefrontal cortex, this information will change the meaning of the sensory inputs from the thalamus, reversing the meaning and therefore the behavioral responses. The sensory input itself arriving into the thalamus, and sent out from there via both the high road and the low road, is not changed. But the meaning attributed to that sensory input is completely transformed by the information provided within the brain from both the high road and the low road as the experience of fireworks becomes familiar and well known to the child to be safe and fun.

In our example, even in the first exposure to the fireworks there was more going on in the child's brain than merely the verbal reassurance given by the adults. The adults held the child close when the fireworks display began. This gave context to the sensory inputs on the first exposure to the

fireworks even though those extreme sensory inputs were utterly without precedent for the child and even though loud noises are one of the few innate fear-generating stimuli for all mammals regardless of their past experiences.

Now let's give this first exposure to fireworks another context. Assume that the adults did not help the child but were busy with their own interests as the time drew near for the fireworks display to begin. Since the adults had no fear of fireworks they simply assumed that the child would not fear them either. Or, even worse, the adults and older children the child revered might laugh at the young child's fear over such an innocent holiday display. Think about how the child would process this experience under those circumstances. Not only would the fireworks be terrifying but the child would feel alone and humiliated. Think of how that child would react to the next exposure to fireworks. In this version of the story, the inputs from both the high road and the low road would not be reassuring. In this scenario we have sensitization to fear reactions incorporated into the brain. In this scenario both the high road and the low road are primed for heightened fear reactions on future exposures that are judged to be similar and that may be generalized beyond just Fourth of July fireworks to include many other potentially frightening experiences.

Before leaving this holiday story, let us do some more changing, this time about the child. When it comes to fears, all three-year-olds are no more alike than are all parents. Some three-year-olds have fear mechanisms that are set on a hair trigger. It does not take much to scare these kids. A child like that might not be fully reassured in the dark as the fireworks are exploding overhead, even by the most considerate and nurturing adult.

Or the child could have been born with a fear mechanism that had a safety lock on the fear trigger. In other words, some children are all but impervious to fear. In these virtually fearless children the LC rarely fires off its signal of danger. In this scenario, even with careless, preoccupied parents this child would be untroubled by even the most dramatic fireworks display.

Here is yet one more observation about this common experience of fireworks: notice how closely related fear and excitement are in the brain. There is often only a slight shift in meaning between something that is terrifying and something that is a joy. The scariest rides at an amusement park have the longest lines of kids wanting to get on them!

Our point here is that no matter how automatic the brain's fear reactions are, when it comes to human experiences, they are not simple. One size does not fit all when it comes to understanding the anxious brain. There is a huge variability in fear reactions among different people—even within a single person at different times. One of the biggest factors governing the brain's fear responses is the meaning attributed to the potentially fear-generating experience. In other words, the cortex is king when it comes to the brain's management of fear.

It is important that you understand the two basic brain pathways for fear because they are both important in understanding anxiety. In this book we especially focus on the role of the cortex, which assigns meaning to sensory experiences, because that is where this book is able to have its greatest effects. The cortex is where all psychotherapy, including cognitive-behavioral treatment, has many of its effects.

Lest we overstate the role of the cortex in anxiety, recall once more our example of the child at the Fourth of July fireworks display. Not all of the reassuring magic was in the adults' words. The human touch was vitally important, as was the context of the child being with trusted adults who were supportive and understanding. Think how different that experience would have been for that child if the "trusted adults" had themselves been afraid of the fireworks or, making this more psychological, if one of the child's parents had been afraid of fireworks but was embarrassed by that fear and therefore had bundled the child off at the last minute saying, "I don't want him to be frightened so I am taking him home now."

In our initial story, sitting in an adult's lap was a big part of what made that fear-reducing experience work. Helpful also was the attention given by the adults, firmly and respectfully reassuring the child in advance to help him or her process the potentially terrifying and disturbing sensory experiences that were to come.

Think again about the experience of that child if the loving adults had not taken the child to the fireworks at all because "the fireworks are too frightening for a child of this age, so we will leave her at home tonight. We don't want her to have to endure that much stress at this age." If that had happened, the child would have learned nothing. In fact the child's fear on subsequent exposures to fireworks could have been magnified by the adult's view that the sounds and sights of fireworks were too stressful for the young child to be exposed to.

Here's yet another take on that fireworks experience. What if the child had been hurt or what if a person the child cared for had been hurt in an

experience that the fireworks would remind the child of? Suppose the child's father had been shot on the front porch, or the child's mother had been injured in a noisy automobile accident. In these terrible cases the child's brain would have already been sensitized to loud noises as signals of real danger. Then the challenges on the Fourth of July for the child and for the adults would have been greater. Our advice would have been the same: Go to the fireworks and help the child manage his or her fears. But the problems faced by both child and adults would have been much more difficult in such situations.

There are many lessons in this exploration of brain biology for anxious people and for those who want to help an anxious person get well. Neither the high road nor the low road is simple or easily managed, even with greater understanding. However, having an understanding of how the brain handles fear helps us think more clearly and more constructively about the common experiences of fear in our lives.

The Neurotransmitters

Having looked at the brain circuitry, the way the brain's neurons are hooked together when it comes to the experience of fear, we need to shift to consider the chemicals by which the brain does its internal communicating. We will also look at how the brain communicates with the rest of the body about fear. Let's focus on the neurotransmitters that are involved in fear and anxiety. Fear can arise from an external threat. Fear can also arise from sensations originating within the body. A severe pain in the chest, for example, which may be interpreted as a heart attack, can lead to fear that is at least as intense as the fear produced by a criminal pointing a gun at your head.

To understand how the brain handles danger, whether the source of that danger is internal or external, you will need to understand these five chemically based brain systems: *the norepinephrine system*, *the serotonin system*, *the dopamine system*, *the corticotropin-releasing hormone system*, and *the benzodiazepine system*. These five chemical systems involve brain anatomy as described above, but instead of focusing on the physical linkages of the neurons, here we focus on the chemical messengers used by the brain to communicate within the brain and with the body as a whole. This chemical focus is important to understanding anxiety because one of the primary ways doctors relate to any illnesses is by using medicines that influence the chemicals inside the body.

Although today doctors do not do much to rearrange the brain's anatomy, they do many things that rearrange the brain's chemistry. Medicines do this without the need of brain surgery. Unlike surgery to rearrange the brain's anatomy, changes made by medicines are reversible. This means that if the patient and the doctor do not like the way a particular medicine works, then the medicine can be stopped and the patient's brain returns to its previous state. This fact is especially important to anxious patients who worry too much about bad outcomes and who often think too little about possible good outcomes, including good outcomes from medical treatments for anxiety. It is reassuring for an anxious patient taking medicine to know that if problems are caused by the use of the medicine, or if the results are less than hoped for, then the medicine can simply be stopped.

The Norepinephrine System

Epinephrine is produced in the two adrenal glands that sit like hats on top of the kidneys. Epinephrine, also called adrenaline, mobilizes the body for acute danger and stress. The epinephrine-related stress-management chemical in the brain is norepinephrine, or noradrenaline. This is the major chemical in the brain that deals specifically with fear. About 90 pecent of the brain's norepinephrine is found in the tiny locus ceruleus (LC), the brain's alarm center. The LC is connected to the neurons in all of the parts of the brain that manage emotions, including the medial prefrontal cortex, the amygdala, and the hippocampus.

When you are frightened, the brain's norepinephrine system swings into high gear, producing changes not only in the brain but throughout your body. For example, temperature, heart rate, and blood pressure all rise when you are frightened. Blood is taken out of the intestines and out of the skin and is put into the muscles to prepare for flight. That is why you turn "white as a sheet" and may feel the need to urinate or defecate when you are very frightened.

The Serotonin System

Serotonin is more widely dispersed in the brain as a neurotransmitter than norepinephrine, but it is also found in many of the same areas as norepinephrine, including the cortex, the amygdala, and the hippocampus. Serotonin receptors are correlated with anxiety. The brain has many

distinct serotonin receptors, some of which increase anxiety and some of which decrease it. The complex serotonin system is the site of some of the most active research in the development of new antianxiety (and antidepressant) medicines. Laboratory animals exposed to stress show increased serotonin activity in their brains.

The Dopamine System

Dopamine is the neurotransmitter most involved in reward, sometimes called "pleasure," and in modulation of mood. Dopamine is closely related to the endorphins, the brain's own pleasure-producing chemicals, which use some of the same brain receptors as are used by opiate drugs such as heroin and morphine. Dopamine is thought to play an especially important role in social anxiety disorder, but because this neurotransmitter is so important in moods it probably has a role in all anxiety problems. Acute stress triggers widespread dopamine release in the brain.

The Corticotropin-Releasing Hormone (CRH) System

Stress, fear, and anxiety all trigger the CRH system located in the hypothalamus, the brain structure that lies below the thalamus. This collection of neurons is located immediately above the pituitary gland, the body's "master gland," which the hypothalamus controls. Studies have not shown elevated levels of CRH in the spinal fluid of patients with some anxiety disorders. However, because the CRH system is so closely related to stress and fear activation in the brain, and because abnormalities in CRH levels have been shown in posttraumatic stress disorder, it is likely that future research will learn more about the specific role of the CRH system in anxiety.

In response to danger, the hypothalamic-pituitary-adrenal axis swings into action with the release of CRH, which triggers the release of cortisol (a major stress-management hormone) and ACTH, which triggers the release of epinephrine and other hormones from the adrenal gland.

The Benzodiazepine System

Approximately 40 percent of the brain's more than 100 billion neurons use the neurotransmitter gamma-aminobutyric acid, or GABA. The highest concentration of GABA receptors in the brain is in the cortical

gray matter, unlike norepinephrine receptors, which are primarily found in the more primitive brain stem. The GABA receptors are part of the benzodiazepine system, so called because this is the system that benzodiazepines influence. The benzodiazepines are a group of closely related medicines including Valium (diazepam), Xanax (alprazolam), and Klonopin (clonazepam). Introduced in the early 1960s, these medicines have proven to be uniquely helpful in the treatment of all of the many manifestations of anxiety, including all of the anxiety disorders. The benzodiazepines increase and prolong the effects of GABA, the brain's primary quieting neurotransmitter.

Because of this powerful antianxiety effect, researchers first identified the benzodiazepine receptor in the brain using this work to understand a great deal more about the biology of anxiety. GABA is the brain's specific antianxiety or antiworry neurotransmitter. Research has shown that people with panic disorder have a smaller number of benzodiazepine receptors than nonanxious people. Animals exposed to chronic stress show reduced benzodiazepine receptor binding, which is, in turn, associated with defects in memory. Chronically anxious animals show reduced ability to think. For example, chronically anxious laboratory rats lose their ability to escape from a maze.

Animals as Teachers about Human Anxiety

Life, often quite literally, depends on the avoidance of danger. This is true from the smallest one-celled organism to the human being. The three minimal requirements for an organism's "fear" are these: (l) a way to detect signals from the environment, (2) a way to identify which of those signals are associated with danger, and (3) a way of escaping from danger. One-celled bacteria, which evolved about 1 billion years ago, meet this three-part test. Bacteria typically have five to seven whiplike flagella that rotate in the same way that propellers work in a boat. Bacteria use their flagella to move in water toward food (such as sugar) and to move away from danger (such as a noxious chemical). Without any nervous tissue, the "learning" of bacteria is limited to simple habituation, with "memory" being restricted to about half a second.

Moving up the evolutionary ladder, mammals split off from their reptilian ancestors during the age of the dinosaurs, about 250 million years ago. One of the major differences between the mammalian brain and the reptilian brain is the much higher development of the limbic system in

the brains of all mammals. This larger limbic system endows mammals with a range of distinctive behaviors. One of the most striking behaviors of mammals is separation anxiety, which is seen in all young mammals and in no reptiles. Infant mammals cry out for their mothers when they are left alone. This remarkable behavior is part of the highly social behavior of mammals. Mammals show intense social attachments—especially the attachments of mothers and infants, which is one of the hallmarks of mammalian behavior.

Infant laboratory rats and mice respond even to their first experienced separation from their mothers with loud calls in a characteristic ultrasonic frequency. In other words, there is no learning or conditioning required for this response. It is innate and universal in young mammals. Later research showed that this crying by the infant rodents was not necessarily a response to movement into a strange setting, to rough handling, or to loud noises. Simply removing the mother and the littermates produced long and loud crying. This experiment showed that it was the loss of social contact that triggered this separation distress. Isolated rat pups learned difficult mazes to regain contact with their mothers. They experienced even short periods of contact with their mothers as strongly reinforcing, and they experienced cues associated with separation from their mothers as strongly and enduringly aversive.

Rat pups learned less well when separated from their mothers except for learning threats of danger or negative cues. The pups were even more responsive to negative cues when separated from their mothers. Experiments with infant rats also showed that when rats reached the equivalence of adolescence, they lost their separation anxiety. Most strikingly, it has been found that medicines that reduce human anxiety also block the separation anxiety of young rat pups. When given Prozac or Valium, infant rats no longer cried out for their mothers when they were left alone. They just quietly (or nonanxiously) waited for their mothers to return.

Researchers investigated whether there were differences between individual rat pups in their sensitivity to separation anxiety. Within five generations of selective breeding, the scientists were able to breed strains of rats that consistently had either high sensitivity or low sensitivity to separation anxiety. This demonstrated clearly the genetic basis of the differences in this trait among rat pups. These researchers are now exploring the differences in the brain chemistry of the two strains of rats and are also looking for other differences in behavior between these two strains.

Much closer to the human brain than the rat's brain is the brain of monkeys, which have 90 to 99 percent of the same genes as humans. One

group of researchers has found a group of wild rhesus moneys living on an island in the Caribbean in which about 20 percent of the monkeys have what appears to be a mild form of generalized anxiety. Infants in this group showed less exploratory behavior. As adolescents, when their mothers left them for hours or even for days during breeding season, these young monkeys showed greater agitation than their nonanxious peers under similar circumstances. When their mothers stayed away a long time, the anxious monkeys showed lethargy and assumed a fetal-like huddled posture associated with social withdrawal. The investigators took these behaviors to be the monkey equivalents of human depression.

The anxiety-prone monkeys had greatly increased sensitivity to inadequate mothering, as when they were experimentally reared with peers instead of with their mothers. This sort of motherless, but otherwise adequate, rearing made their anxiety symptoms worse. On the other hand, the physical, motor, and many social behaviors in these anxious moneys developed normally. The anxious young monkeys had a strong tendency toward anxious withdrawal and avoidance of novel experiences that increased as they became young adults. The anxious monkeys dropped to the bottom of the social hierarchies within the monkey colonies. Importantly, if these biologically anxious monkeys were raised as infants by unusually nurturtant and experienced mothers, then the expression of their anxious traits was entirely prevented.

These animal models of anxiety show that anxiety traits are heritable. The high levels of anxiety traits seen in these wild animal communities provide an opportunity for natural selection to act upon these traits. This suggests that in many environments there are selective advantages to at least modest levels of anxiety, especially when the population is subject to harsh and dangerous conditions. This animal research also underlines the importance of mothering in the expression of anxious traits. In the human context it offers real hope that early identification and intervention with anxious children can prevent the expression of many of the more maladaptive expressions of anxiety later in life.

The separation anxiety calling response of infant mammals is similar to the behaviors seen in very young birds. In the species where this behavior has been studied, the infant crying for the lost mother has shown to be remarkably similar to the phenomenon of agoraphobia in humans, which has been called "adult separation anxiety."

These are exciting times for everyone concerned with the problems of anxiety. Never before has so much attention been focused on anxiety and

never before have there been so many good treatments for people with anxiety. It is impressive that so many talented people are today working hard to understand anxiety and to find new treatments for it. Even better, there is every reason to expect that the pace of discovery of new and better treatments for anxiety will increase in coming years with improved understanding of the biology of the anxious brain.

The picture of the anxious brain outlined in this chapter will be expanded in the discussion of medicines in Chapter 4. In that chapter we will zero in on the neurotransmitter systems that manage anxiety and see how medicines normalize the disturbed chemistry of the anxious brain. Most remarkably of all, in recent years scientists have learned that the anxious brain's chemistry can be changed not only by using medicines—by adding highly specific chemicals to the brain's environment—but also by changing thoughts and behaviors. It will come as no surprise that thoughts and behaviors reflect chemical events in the brain. Recognition that the anxious brain's disturbed chemistry can be normalized by specific changes in thinking and behaving is both new and gratifying. Healing strategies that do not involve medicines have been organized into the form of psychotherapy called cognitive-behavior treatment. The biology of the anxious brain is important for understanding not only how medicines work but also how CBT works.